Armed Forces College of Medicine

AFCM

Rheumatic fever: An immunological insight

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INTENDED LEARNING OBJECTIVES (ILO)

- **By the end of this session the student will be able to:**

1. **Outline the aetiology of rheumatic fever**
2. **Describe the pathogenesis of the disease**
3. **List the important lesions and clinical manifestations**
4. **Define the important diagnostic features & lab findings in rheumatic fever**

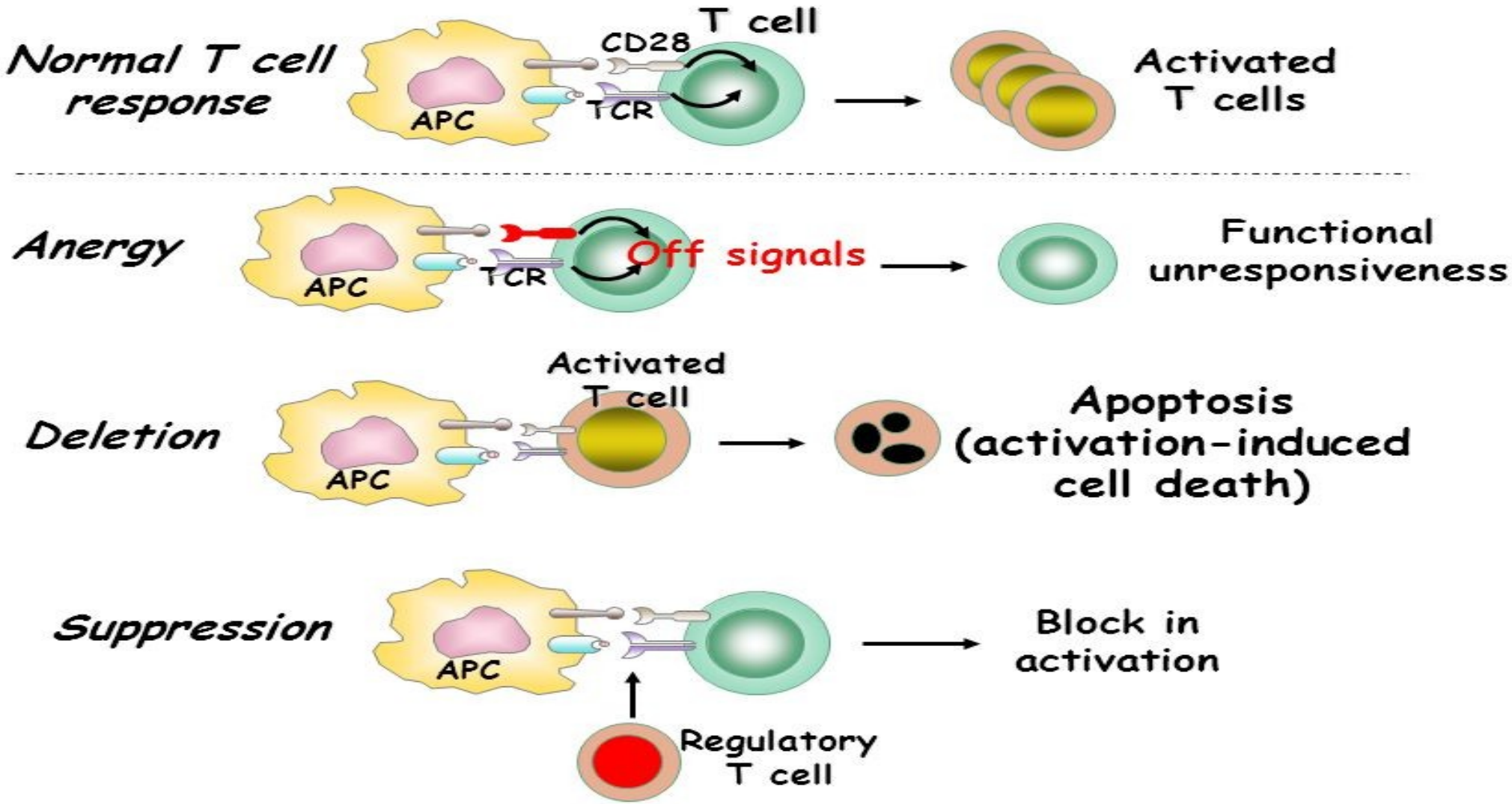
Definitions

- **Autoimmune disease:** **Adaptive IR attacking own body tissues**

Occurs due to failure of tolerance

- **Heterophil Antigen**
- **Molecular Mimicry**
- **Central & Peripheral tolerance**

Peripheral tolerance



In a nut shell

- **Immune tolerance:**

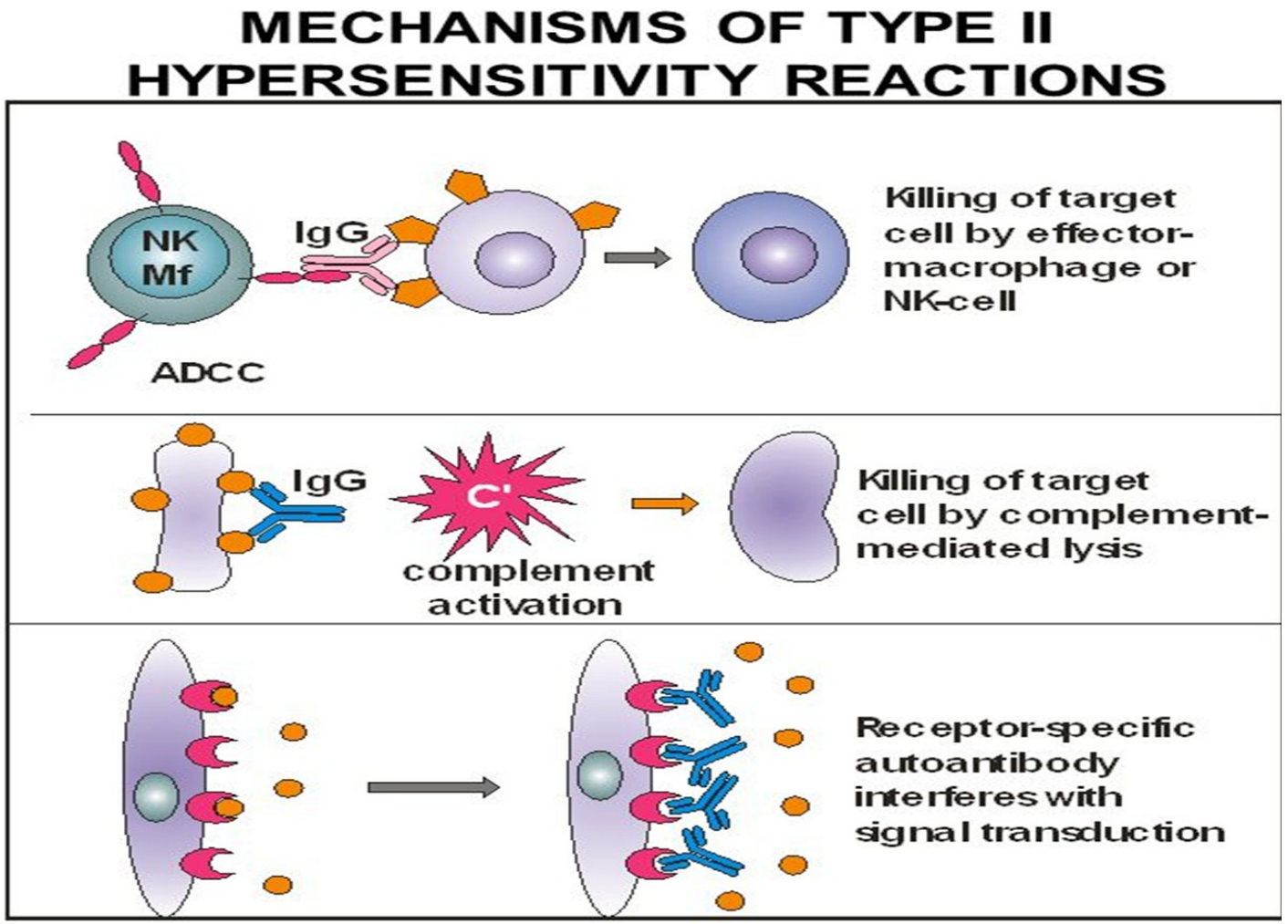
Central: Clonal deletion/ receptor editing

Peripheral:

- ✓ **Clonal anergy**
- ✓ **Clonal ignorance**
- ✓ **Deletion**
- ✓ **Suppression by T regulatory cells**



Type II Hypersensitivity reactions

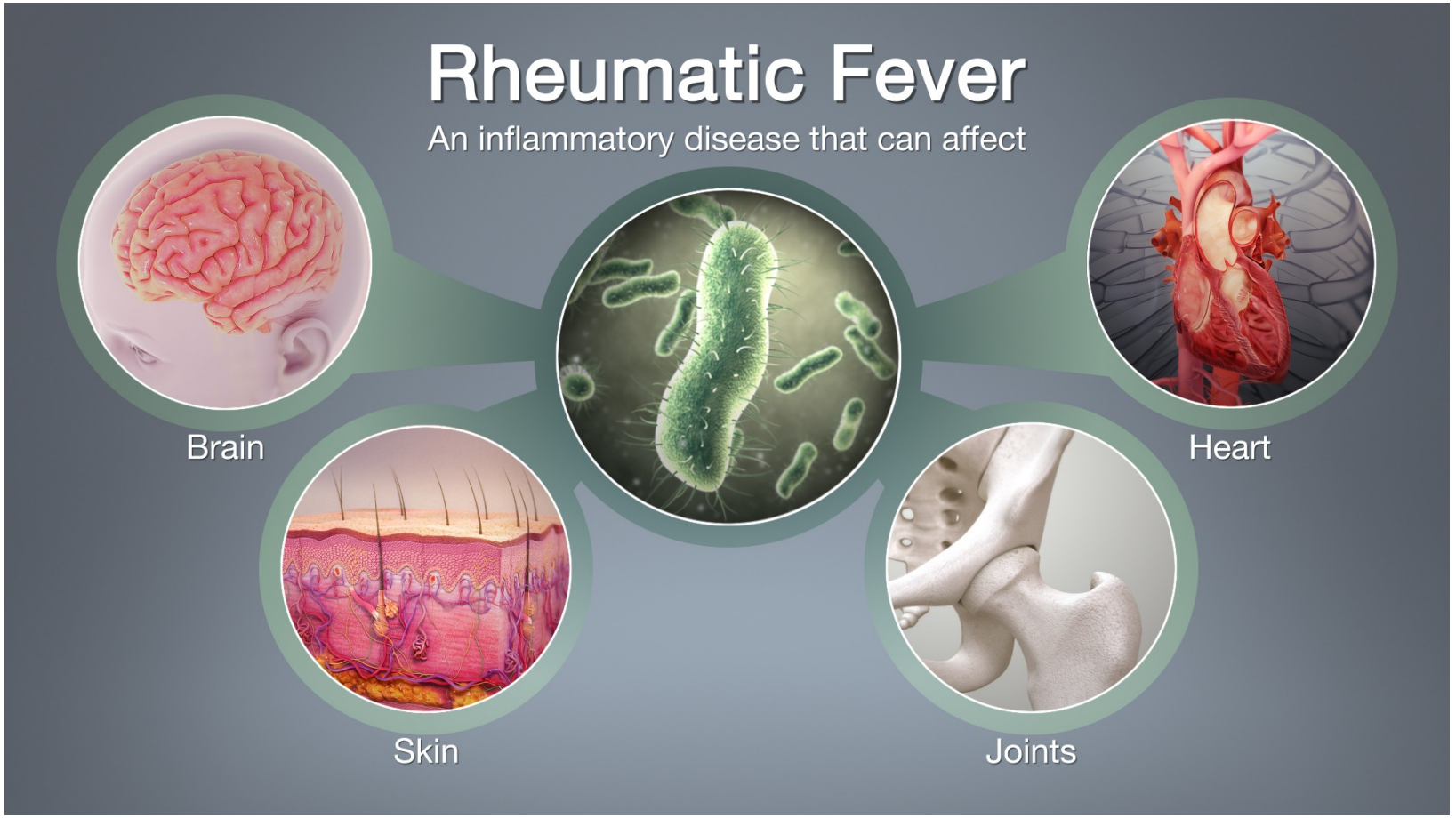


Quiz

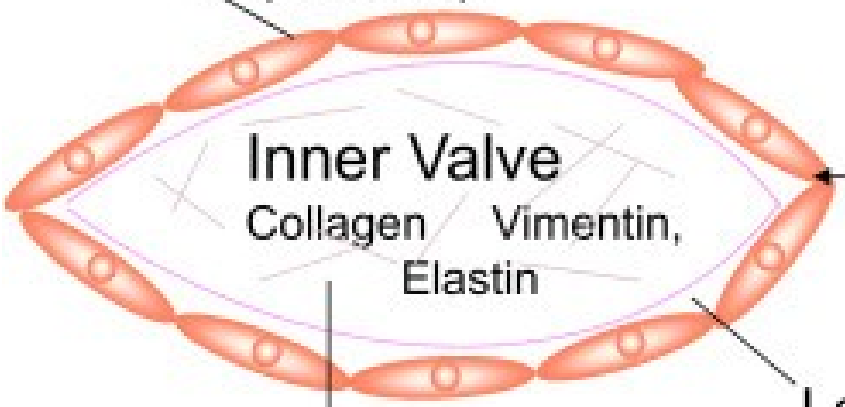
- Which of the following organisms is involved in the pathogenesis of rheumatic fever?

a. *Streptococcus pyogens*
b. *Streptococcus agalactiae*
c. *Staphylococcus aureus*
d. *Streptococcus pneumoniae*
e. *Staphylococcus epidermidis*

Type II Hypersensitivity reactions



Rheumatic Heart Disease
Valve Model



- **Antibody** binds endothelium
- **VCAM-1** activated endothelium attracts T cells

- **T cells** extravasate through endothelium (Mimicry)
- **Th1/Th17** response

Laminar Basement Membrane (Laminin) → Exposed due to Endothelial damage

- Breakdown of internal valve proteins; cardiac myosin at valve insertion in myocardium; chordae tendinae damaged

- Avascular valve becomes neovascularized

Molecular Mimicry

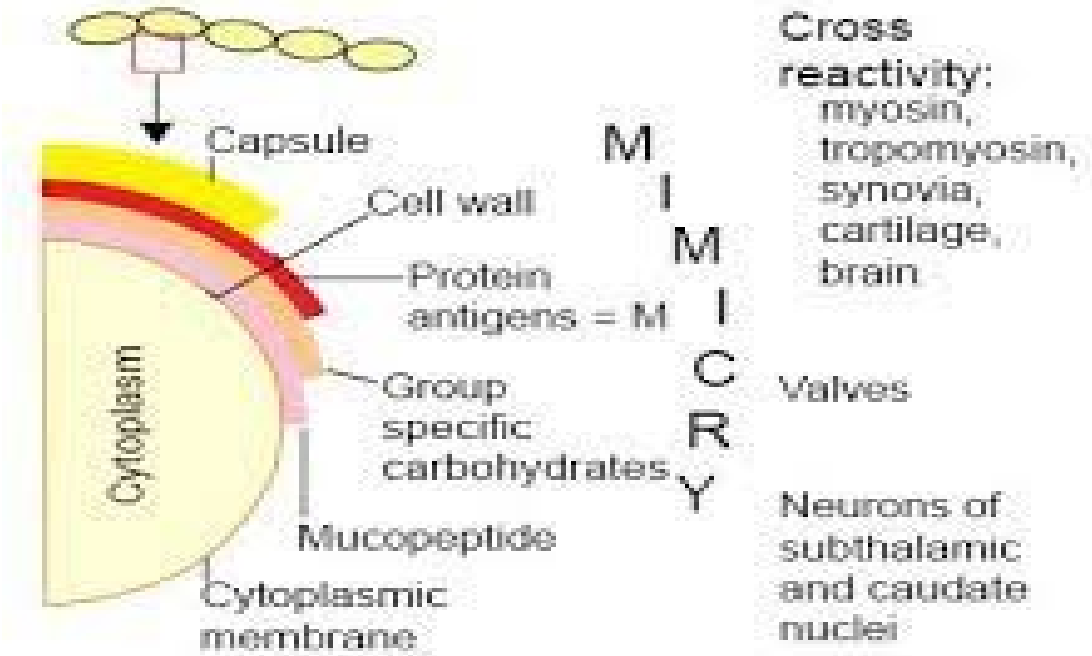
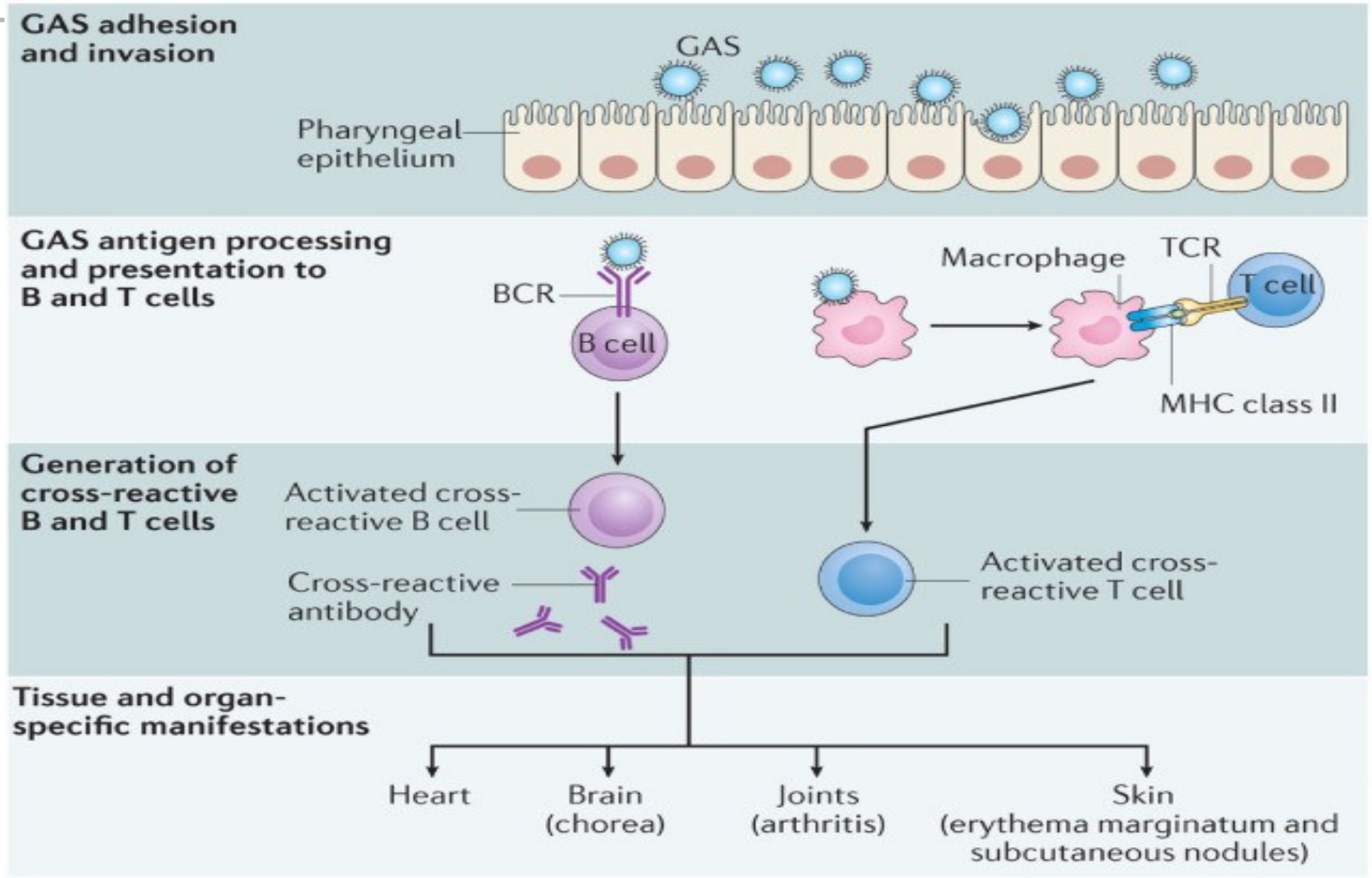


Fig. 4 : Diagram showing Molecular Mimicry in Acute Rheumatic Fever. Similarity between streptococcal cell wall antigens with endogenous antigens in cardiac tissue, synovium, cartilage and brain leads to immunologic attack by the host antibodies and manifestations of acute rheumatic fever.

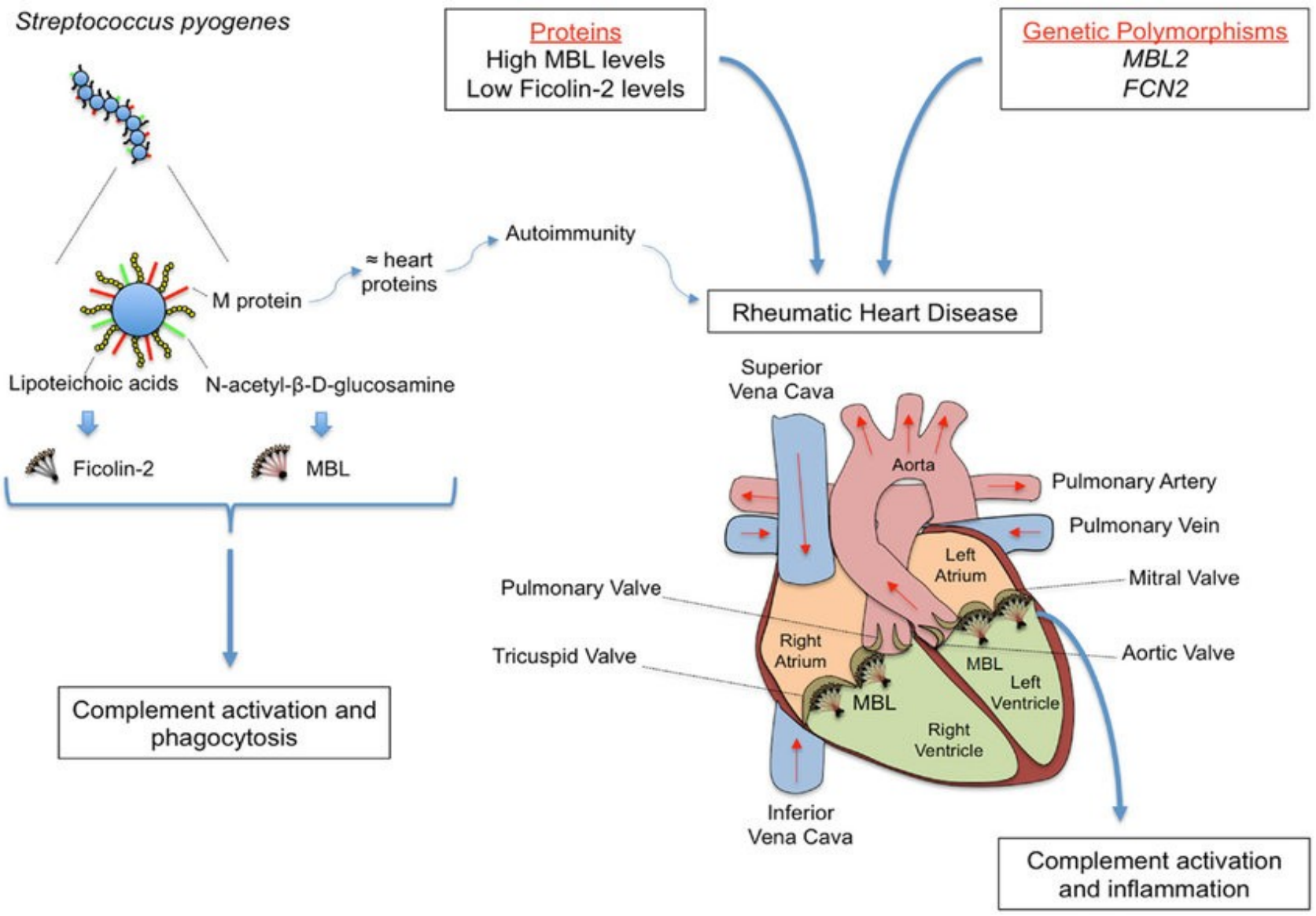
- ***Heterophile antigens*** are a group of similar antigens found in unrelated animals, IE, man, sheep, horse, dog cat, mouse.
- ***Heterophile antibodies*** produced against heterophile antigens of one species will cross react with others.

Molecular mimicry

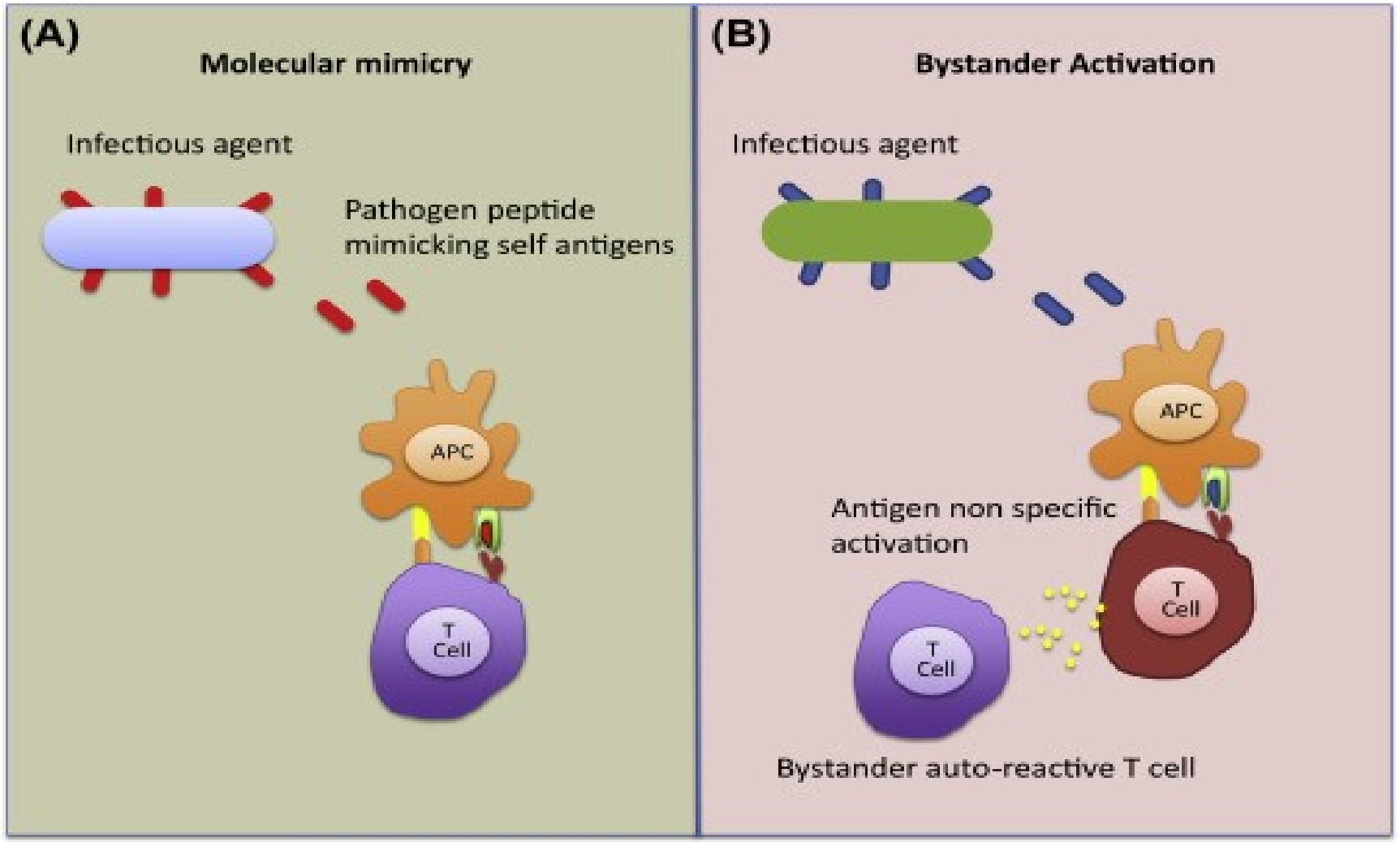


Nature Reviews | Disease Primers

Mechanism of tissue damage

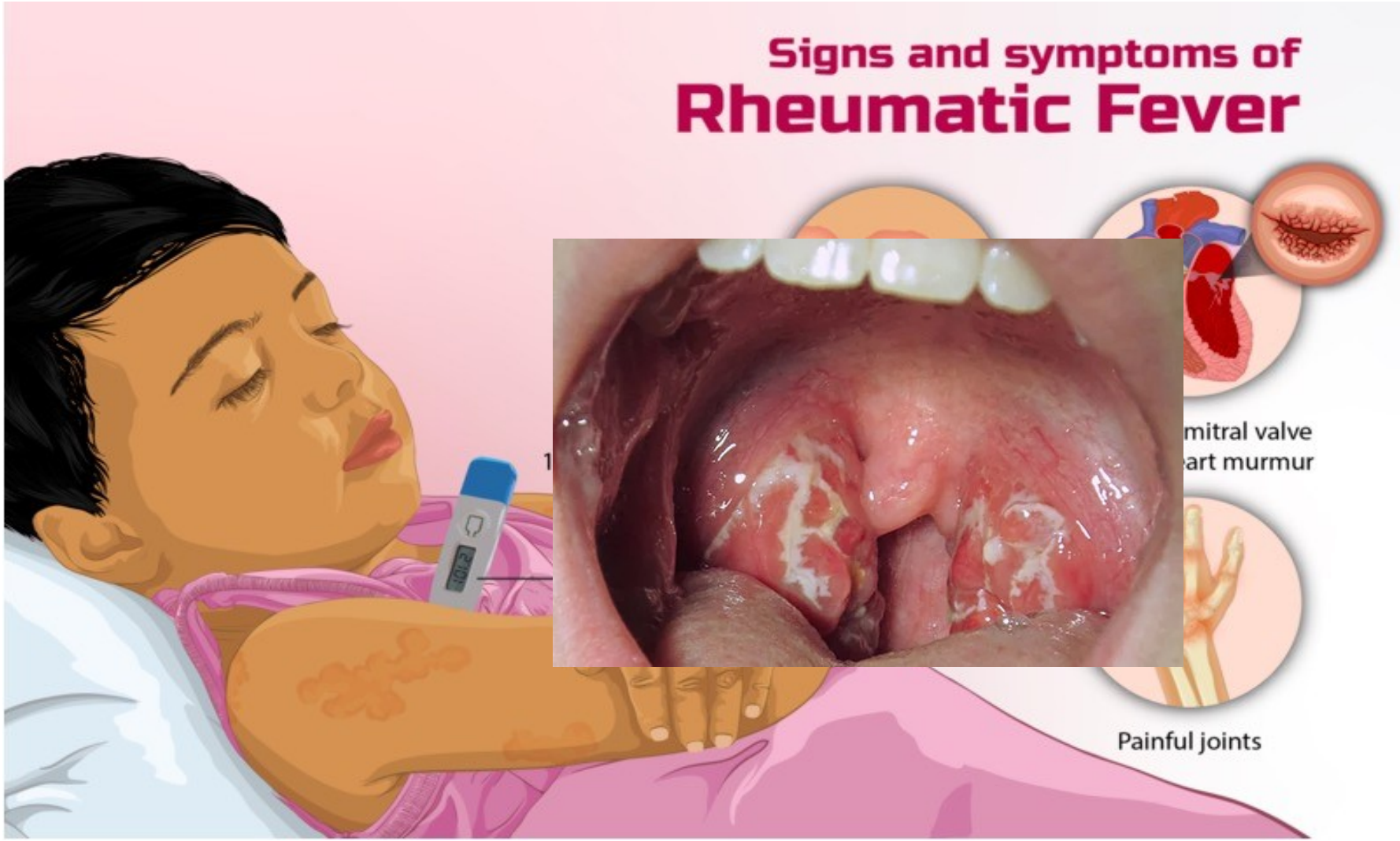


Molecular mimicry Vs Bystander activ

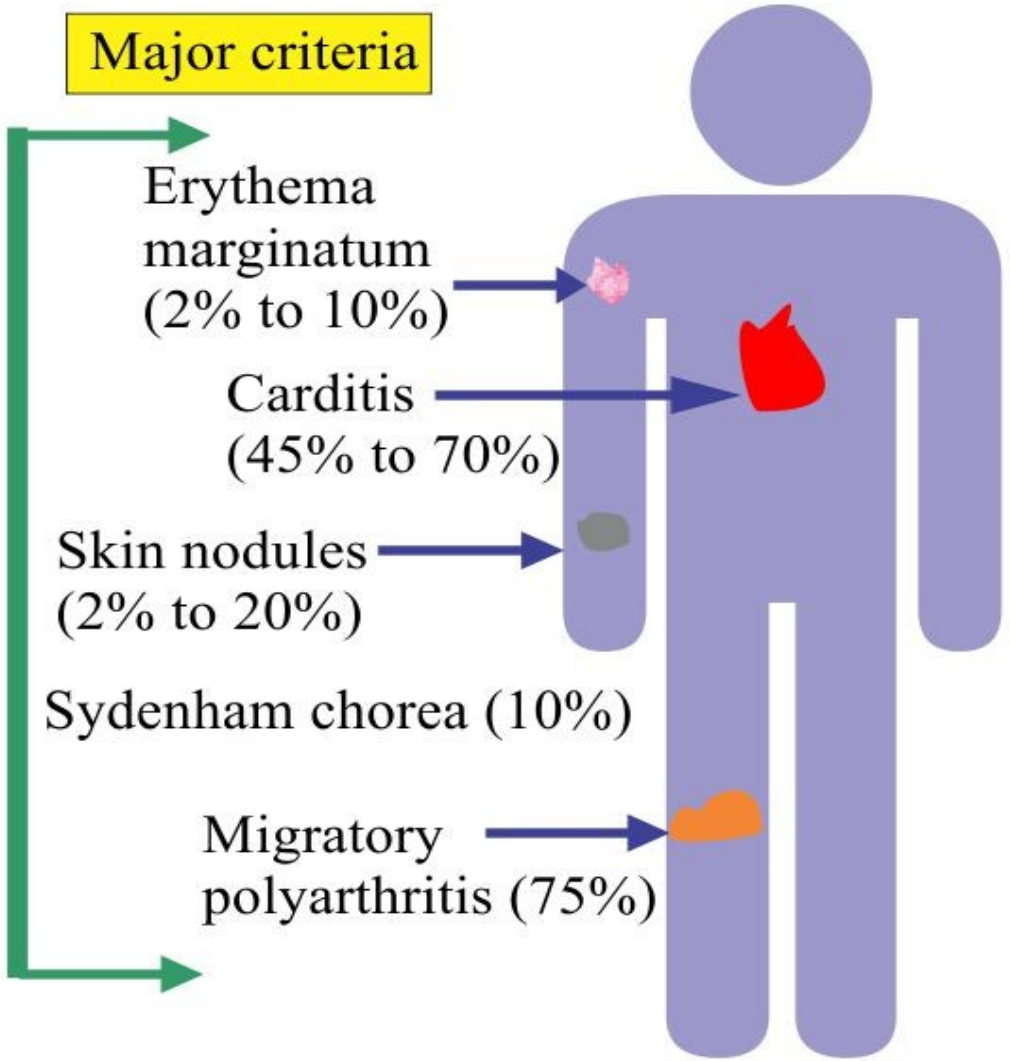



BREAK TIME

Signs & Symptoms



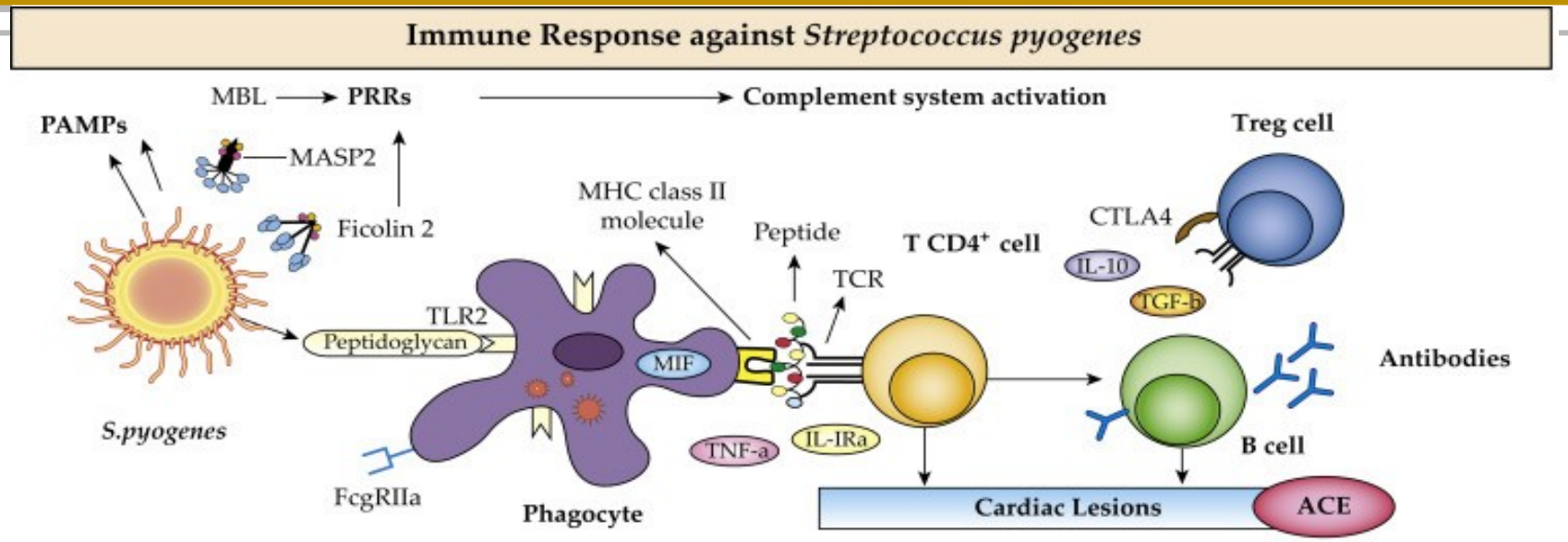
Diagnosis



Minor criteria

1. Fever
2. Arthralgia
3. Raised ESR
4. Raised CRP
5. Prolonged PR-interval
6. H/O Rheumatic fever or Rheumatic heart disease

Immunological mediators role in Rheumatic fever



Genes and their role

Pathogen Recognition and Complement System Activation

MBL2 - recognizes mannose and N-acetylglucosamine in pathogens
MASP2 - protease; lectin pathway
FCN2 - codifies Ficolin 2; carbohydrate binding; opsonic activities

Pathogen Recognition and Phagocytosis

TLR2 - pathogen recognition (lipoproteins); activation of innate immunity
FCGRIIA - phagocytosis and clearing of immune complexes
MIF - macrophage migration inhibitory factor; macrophage function

Antigen presentation to T cells

HLA-DRBI, HLA-DQAI, HLA-DQBI - presenting peptides derived from extracellular proteins

Proinflammatory Cytokines

TNFA - proinflammatory cytokine
IL-1RA - inhibits the IL-1 function ; IL-1 inflammatory responses

Immune Response Control

CTLA4 - inhibitory signal to T cells
IL-10 - immunoregulation
TGFBI - regulates cell proliferation, differentiation, migration

Cardiac Tissue Damage Progression

ACE - enzyme; conversion of angiotensin I into a physiologically active peptide angiotensin II.

Quiz

Which of the following represent the main mechanism of tissue damage in Rheumatic fever?

a. cross-reactivity of pathogen and self antigens.

b. expression of self antigen in the thymus or bone marrow.

c. low avidity presentation of some self peptides in the thymus.

d. random generation of TCR and BCR specificities.

e. tissue injury which releases normally hidden self antigens.

Diagnosis of Rhematic fever

- Rheumatic fever is mainly a clinical diagnosis
- *No single diagnostic sign or specific laboratory test available for diagnosis*
- Diagnosis based on MODIFIED JONES CRITERIA

✓ Jones Criteria – Diagnosis of ARF requires **2 major criteria** OR **one major and two minor criteria** + evidence of recent streptococcal infection

Laboratory findings



- **Throat culture**
  - Throat culture findings for group A beta hemolytic *Streptococcus* are usually negative by the time symptoms of rheumatic fever or rheumatic heart disease appear.
- **Rapid antigen detection test**
  - This test allows rapid detection of group A streptococcal antigen and allows the diagnosis of streptococcal pharyngitis and the initiation of antibiotic therapy while the patient is still in the physician's office.

Laboratory findings

Antistreptolysin O titer (ASO)

Positive titre: >200 IU/mL

- Detects antibody to the antigen streptolysin O produced by group A streptococci. Titer rises to a peak at 4-6 weeks and may remain elevated for 1 year.

Positive in:

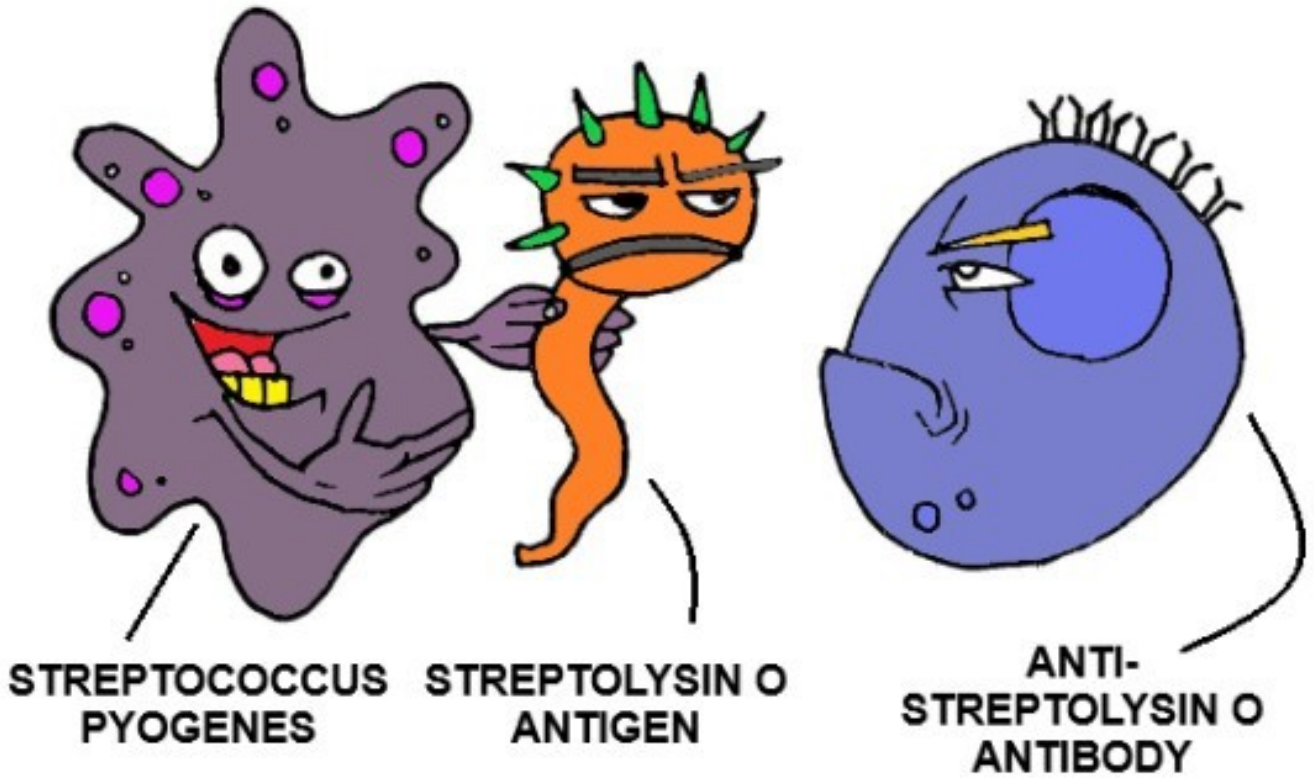
- Streptococcal infection (eg, upper airway infections, scarlet fever)
- post-streptococcal infection complication (eg, glomerulonephritis and rheumatic fever).

False positive in

- Some bacterial infections.



Laboratory findings



Quiz

Which of the following denotes a laboratory finding in Rhematic fever supporting the diagnosis?

a) Chorea

b) Positive anti-streptolysin O titer

c) PCR

d) Prozone phenomenon

e) Throat culture

SUGGESTED TEXTBOOKS

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1. ***Review of Medical Microbiology and Immunology, Warren Levinson Chapter 66 p. 1214: 1231***
2. ***Cellular and molecular Immunolgy , Abul Abbas & Lichtmann Chapter 15 p.315:335***


THANK
YOU